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(21) International Application Number: PCT/GB00/00707 (22) International Filing Date: 29 February 2000 (29.02.00) (30) Priority Data: P990100866 1 March 1999 (01.03.99) AR (71) Applicant (for all designated States except IS US): ETHICAL PHARMACEUTICALS SOUTH AMERICA S.A. [AR/AR]; Avenida San Juan 2266, 1232 Buenos Aires (AR). (71) Applicant (for IS only): PAGET, Hugh, Charles, Edward [GB/GB]; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): STEFANO, Francisco, José, Evaristo [AR/AR]; José Maria Gutierrez 3950 3A, 1425 Buenos Aires (AR). SCASSO, Alejandro, Fabio [AR/AR]; Florencio Varela 1404 Lanus Oeste, 1824 Provincia de Buenos Aires (AR). GABACH, Roberto, Juan [AR/AR]; Avenida Las Heras 2949 6A, 1425 Buenos Aires (AR). (74) Agents: PAGET, Hugh, C., E. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: TRANSDERMAL DEVICE COMPRISING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCORPORATED IN ACRYLIC ADHESIVE POLYMER MATRIX		
(57) Abstract This invention pertains to transdermal administration devices, and more particularly, to transdermal administration devices that contain: (a) a pharmaceutical composition for the systemic administration of a NSAID; (b) a backing layer; and, (c) a release liner; wherein said pharmaceutical composition includes at least one component that enhances percutaneous permeation selected from: (i) fatty alcohols (C ₄ -C ₃₀); (ii) mono, di or triglyceryl fatty acid esters (C ₄ -C ₃₀); and, (iii) fatty acid esters (C ₄ -C ₃₀); and a pressure sensitive acrylic adhesive matrix formed by a copolymer with polar functional groups in which the NSAID is incorporated.		

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site.

Also, patent EP 524582 B1 discloses the composition of a diclofenac sodium plaster that comprises a penetration enhancer composed of 1-menthol and propylene glycol, for which the authors claim a
5 good percutaneous absorption of the active drug.

Patent US 4,738,848 discloses an adhesive preparation comprising a flexible support which contains a combination of diclofenac sodium and an
10 organic acid that facilitates the solubilisation of the active drug and its percutaneous absorption.

However, the previous patents appear to be restricted to effects nearby the site of action and do not mention any general or systemic therapeutic effect,
15 nor do they present experiments in human related to such mentioned systemic action of the topical applied active drug. Thus, the uses described in the aforementioned patents would be limited to the treatment of local diseases in the vicinity of the site
20 of application.

In spite of the fact that in many patents the transdermal administration of anti-inflammatories is mentioned (EP 379,045 B1, US 5,662,925, US 5,674,521, US 5,336,213, US 5,132,115), there are no references or
25 specific teachings to evaluate the efficacy of the disclosed products (devices) or the methodologies relating to the manufacture of those products (devices).

Patent US 4,999,379 discloses the systemic
30 administration of diclofenac through a transdermic composition that specifically contains two permeation enhancers, N, N-dimethyl-lauroylamide or 1-N-dodecylazacycloheptan-2-one. In its examples related to matrix patches, the active drug is micro-suspended,
35 which means that its absorption from the matrix could

be erratic, since it is not solubilised. On the other hand, it does not claim the systemic effect achieved by the release of low and steady concentrations of the active drug. Also, it does not indicate the use of acrylic adhesive or the permeation data of the drug released from the transdermic device. Moreover, no indication of the plasmatic levels reached or the therapeutic effects are informed.

Patent US 5,665,378 is related to the transdermal administration of several NSAIDs (including diclofenac sodium), capsaicin and pamabrom, using menthol, eucalyptol, glyceryl monostearate and d-limonene as permeation enhancers. This patent discloses a reservoir type transdermal system and does not claim the presence of steady plasmatic concentrations to yield systemic effects.

Patent EP 827741 A2 discloses a composition for the transdermal release of a NSAID such as propionic acid derivatives (ketoprofen, etc.), wherein the drug is dispersed in non-polar adhesive polymers, in which an increase of the skin permeability is found because of the different physico-chemical characteristics that exist between these drugs and the mentioned adhesives. This patent does not have information related to the systemic effect of the device, plasmatic concentrations or experiments of therapeutic efficacy.

The anti-inflammatory reaction is recognised as a defence mechanism of the body against external or internal aggressions. It is initiated by the local secretion and release of several compounds synthetised by the cells involved in the defence reaction as interleukines, bradykinin, and prostaglandins. The pharmacological action of currently available NSAIDs is related to inhibition of the enzyme cyclooxygenase, which transforms a fatty acid present in the cell

membranes (arachidonic acid) to intermediates that will result in different types of prostaglandins that initiate and maintain the anti-inflammatory response. [1]

5 The inhibition of this enzyme could be irreversible, as the one produced by acetylsalicylic acid or competitive as the one produced by ibuprofen. In the first case the exposure of the enzyme at low concentrations of the inhibitor for a long time, will
10 yield a degree of inhibition similar to the one obtained when the enzyme is exposed to high concentrations of the inhibitor for short periods of time. In contrast, for the competitive inhibitors, the amount of inhibition is a function of the concentration
15 of the anti-inflammatory and it is independent of the time of exposure.

Summary of the Invention

20 We have found that for a set of non-steroidal anti-inflammatory drugs, as diclofenac, piroxicam, indomethacin, and meloxicam, the enzymatic inhibition of the cyclooxygenase, measured as the anti-inflammatory response, can be achieved if the pharmaceutical composition releases low and steady
25 plasmatic concentrations of NSAID (constantly) and for prolonged periods of time. The described release is obtained if the NSAIDs are dissolved in an autoadhesive matrix of an acrylic copolymer comprising polar groups and adding to the compositions compounds that control
30 the percutaneous permeation. Consequently, in this manner, the obtained pharmaceutical composition has simultaneously the therapeutics advantages of the oral administration of the NSAID and the low incidence of side effect attributed to the local dosage forms.
35 Additionally, this invention has the well-known

advantages of transdermal systems.

Many strategies have been suggested to overcome the low skin permeability of NSAIDs and it is very well known that the selection of suitable vehicles is an important factor in the percutaneous absorption of the drug.

In our invention, the combination of the NSAID with already known compounds that modify the skin permeation, such as fatty alcohols (C_4 - C_{30}), mono, di or triglyceryl fatty acids esters (C_4 - C_{30}) or fatty acid esters (C_4 - C_{30}), in a matrix type transdermic device (in which the matrix is an acrylic pressure sensitive adhesive copolymer with polar functional groups), yields a suitable permeation of the active drug.

The novelty of our invention consists in the achievement of lower and steadier plasmatic concentrations than those obtained with other systemic pharmaceutical dosages, being these concentrations able to yield similar therapeutic efficacy than the other dosage forms with a decrease of undesirables effects. So, it is not our objective to obtain high permeation fluxes of the drug to yield therapeutic efficacy, because we have unexpectedly found that it is possible to perform a therapeutic effect by the maintenance of low and steady plasmatic concentration of the active drug trough the whole period of administration.

It is, therefore, an object of this patent to describe compositions of non-steroidal anti-inflammatory drugs in combination with modifiers of the percutaneous permeation in transdermal systems in which the pressure sensitive polymeric adhesive matrix has polar functional groups, that have the property of producing steady plasmatic concentrations of the active drug capable to obtain a systemic anti-inflammatory and analgesic effect and avoiding the limitation of its use

only in the vicinity of the affected structure (joint or muscle).

Summing up, in the present invention we describe compositions comprising NSAIDs in combination with modifiers of the percutaneous permeation that are incorporated into pressure sensitive adhesive polymeric matrix with polar functional groups, which have the property of releasing steady plasmatic concentrations of the active drug capable to obtain a systemic effect and avoiding the limitation of its use only in the vicinity of the affected structure (joint or muscle).

Detailed Description of the Invention

In the transdermal device described in the present invention, a NSAID such as diclofenac, piroxicam, indomethacin, meloxicam, or a pharmaceutically acceptable salt thereof, is the active drug, which is dissolved and incorporated homogeneously into the adhesive polymeric matrix. It is especially important to take into account the compatibility of the active drug with the polymeric matrix in the process of preparation of the mixture in order to guarantee the physical and chemical stability of the product.

The preferred concentration of the active drug is between the 4.5 and the 32% by weight of the polymeric matrix.

Also, modifiers of the percutaneous permeation which facilitate the dissolution or modify the properties of the stratum corneum modulating the transfer of the NSAID to the circulation, are added. These type of substances may be selected from fatty alcohols (C_4 - C_{30}), mono-di or triglyceryl fatty acid esters (C_4 - C_{30}), and fatty acid esters (C_4 - C_{30}) (i.e., esters of a fatty acid (C_4 - C_{30}) and an alkanol (C_{1-8} , preferably C_{1-4})), preferably with a concentration not

higher than 35%, because an excess of these compounds decreases the adhesive properties and may produce irritation of the skin.

As for pressure sensitive adhesives, we have selected those with polar functional groups.

Particularly preferred are those polymers with a predominance of carboxylic acid groups and minimal presence of hydroxyl groups and there is little or no need of addition of cross-linking agents (as organic salts of transition metals). Examples of such adhesives include polyacrylate adhesives, which are produced by the copolymerization of acrylic acid, acrylic esters, and other functional monomers.

The preferred adhesives used for the invention are sold by National Starch & Chemical Company, but the use of adhesives from other companies with similar characteristics is also possible as would be known by anyone skilled in the art. Examples of suitable adhesives include the following, from National Starch & Chemical Company:

DT 87-2852, which contains:

2-ethylhexylacrylate: 65% (primary monomer);
methyacrylate: 28% (modifying monomer);
acrylic acid: 7% (monomer with functional group);
aluminum acetylacetonate (crosslinker);
functional group: -COOH.

DT 87-2353, which contains:

2-ethylhexylacrylate: 62% (primary monomer);
methyacrylate: 32% (modifying monomer);
acrylic acid: 6% (monomer with functional group);
glycidylmethacrylate: <1%;
functional group: -COOH.

DT 87-2070, which contains:

2-ethylhexylacrylate: 64% (primary monomer);
vinyl acetate: 35% (modifying monomer);
acrylic acid: 1% (monomer with functional
group);
5 2-hydroxyethylacrylate: <1% (monomer with
functional group);
aluminum acetylacetonate (crosslinker);
functional group: -COOH/-OH.

10 Because of the general characteristics of these
types of combinations, the protection against oxidation
using antioxidants and stabilising agent as
butylhydroxytoluene, butylhydroxyanisol, ascorbic acid,
tocopherols, lecitin, polyvinyl pyrrolidone, gum guar,
15 or carboxymethylcellulose may be necessary.

Sometimes, the addition of fillers, such as
bentonite, titanium dioxide, talc, or silicon dioxide
has been useful, but the concentration of filler is
preferably lower than 7.5%.

20 The transdermal system, typical of this
invention, is obtained when a homogeneous mixture is
obtained from the combination of the aforementioned
compounds. The obtained mixture is coated (with a
thickness preferably no greater than 425 μm) onto a
25 polyester, cellulose acetate, polyvinyl chloride,
polyethylene, metallised polyethylene liner or
siliconized or fluoropolymerized or properly treated
vinyl-ethylene acetate copolymer in order to have a
non-adhesive phase.

30 The coated film is then dried in a continuous
processing oven. The conditions in the drying process
are adequate to produce an homogeneous evaporation of
the solvents avoiding the presence of solvent trapped
into the polymeric matrix, which can cause bubbles,
35 craters or folds that can alter the aesthetic

appearance. The residence time in the oven is optimised so as not to alter or degrade any of the components or the structure of the liner but assure the complete curing of the used adhesive. Typically, the conditions to fulfil the former objectives are temperatures lesser to 110°C and residence times less than 12 minutes.

After its exit from the oven, the structure that contains the dry adhesive is laminated with the backing liner. Suitable materials for the backing liner include polyethylene, polyester, vinyl-ethylene acetate copolymer, polyurethane, polyvinylalcohol copolymer, non woven fabrics, or multilayer films of the mentioned materials.

The multilayered laminate is conveyed into rolls of suitable size and taken to a die-cutting machine, which may be rotary or any other suitable type. By using suitable cutting tools it is possible to obtain transdermal devices of a variety of shapes and active surfaces in order to assure effective dosages of the active drug. The obtained transdermal devices are conditioned in their final packaging.

The devices that are the objects of this invention are preferably applied on non-irritated skin areas and free of hair (i.e. shoulders, forearms, arms, chest, abdomen, gluteal, etc.). Preferably, they are not applied in areas of the body where the stratum corneum is thick (i.e. palm of hand, sole of the foot).

Examples 1 to 20 describe compositions based on this invention, in which the composition of the formula is expressed as percent of the weight of the total content of the dry coating, i.e. excluding adhesive solvents.

Examples 21 to 25 show experimental results that illustrate permeation, plasmatic concentrations

and systemic effect of the compositions in humans.

Examples 22 to 24 demonstrate that the invention achieves an evident improvement of the evaluated parameters, essentially pain, in which it is similar to the reported for the oral dosages of several NSAIDs.

In Example 25, it is observed that the plasmatic concentrations of the active drug achieved with our invention are steady over the application period of 24 hours and they are much lower than the ones achieved with oral or injectable preparations in accordance with the pharmacokinetics data found in bibliography.

All this sustains the novelty of our invention, in which an efficacy similar to other systemic dosage form is achieved, but with low and steady levels of the active drug in the blood.

Example 1

A mixture of 79.45 parts of adhesive, 10 parts of NSAID, 10 parts of permeation modifier and 0.55 parts of antioxidants are slowly mixed with stirring to minimise the incorporation of air. It is feasible that an increase of the temperature of the mixture be necessary to dissolve the components. The obtained mixture is coated onto the release liner, dried and then covered with the backing layer. The resulting composition has the following compounds in the indicated quantity:

Compound	%
Adhesive DT 87-2852	79.45
Diclofenac diethylammonium (DDA)	10
Isopropyl myristate (IPM)	10
Butylhydroxytoluene (BHT)	0.5
Butylhydroxyanisol (BHA)	0.05

In the following examples the method of example 1 is used with the appropriate starting material to obtain compositions with the following compounds:

Example 2

Compound	%
Adhesive DT 87-2852	60
DDA	15
Oleyl alcohol (OA)	25

Example 3

Compound	%
Adhesive DT 87-2353	79.45
DDA	10
IPM	10
BHT	0.5
BHA	0.05

Example 4

Compound	%
Adhesive DT 87-2852	64.45
DDA	25
OA	10
BHT	0.5
BHA	0.05

Example 5

Compound	%
Adhesive DT 87-2852	64.45
DDA	25
Glyceryl monooleate (GMO)	10
BHT	0.5
BHA	0.05

Example 6

Compound	%
Adhesive DT 87-2353	64.45
DDA	25
GMO	10
BHT	0.5
BHA	0.05

Example 7

Compound	%
Adhesive DT 87-2852	63.45
DDA	25
GMO	10
BHT	0.5
BHA	0.05
Polyvinylpyrrolidone (PVP K-30)	1

Example 8

5

Compound	%
Adhesive DT 87-2852	59.45
DDA	25
GMO	10
BHT	0.5
BHA	0.05
Bentonite NF	5

10

Example 9

15

Compound	%
Adhesive DT 87-2353	59.45
DDA	25
GMO	10
BHT	0.5
BHA	0.05
Bentonite NF	5

20

25

Example 10

Compound	%
Adhesive DT 87-2353	64.45
Indomethacin (IN)	25
GMO	10
BHT	0.5
BHA	0.05

30

35

Example 11

Compound	%
Adhesive DT 87-2353	76.95
IN	12.5
GMO	10
BHT	0.5
BHA	0.05

40

15

Example 12

5

Compound	%
Adhesive DT 87-2852	64.45
IN	25
GMO	10
BHT	0.5
BHA	0.05

10

Example 13

15

Compound	%
Adhesive DT 87-2353	76.95
IN	12.5
GMO	10
BHT	0.5
BHA	0.05

20

Example 14

25

Compound	%
Adhesive DT 87-2852	74.45
Piroxicam	15
OA	10
BHT	0.5
BHA	0.05

30

Example 15

35

Compound	%
Adhesive DT 87-2353	74.45
Piroxicam	15
OA	10
BHT	0.5
BHA	0.05

40

16

Example 16

Compound	%
Adhesive DT 87-2852	74.45
Piroxicam	15
GMO	10
BHT	0.5
BHA	0.05

Example 17

Compound	%
Adhesive DT 87-2353	74.45
Piroxicam	15
GMO	10
BHT	0.5
BHA	0.05

Example 18

Compound	%
Adhesive DT 87-2070	69.45
DDA	15
GMO	15
BHT	0.5
BHA	0.05

Example 19

Compound	%
Adhesive DT 87-2070	71.95
IN	12.5
IPM	15
BHT	0.5
BHA	0.05

Example 20

Compound	%
Adhesive DT 87-2070	71.95
Piroxicam	12.5
IPM	15
BHT	0.5
BHA	0.05

Example 21

Permeation experiments through mouse skin were performed using the transdermal device obtained as in Example 4 and a commercial plaster of local action (Dioxaflexâ, lot 960212, made in Switzerland), which results are in Table 1:

TABLE 1

Time (hours)	Amount of permeated diclofenac (cumulative) ($\mu\text{g}/\text{cm}^2$)	
	Dioxaflex	Transdermal device according to Example 4
4	1.29 \pm 0.38	4.82 \pm 0.53
8	3.28 \pm 0.93	24.29 \pm 4.94
24	13.02 \pm 4.91	80.36 \pm 6.52

This comparative experiment shows the higher permeation of the product elaborated as in Example 4.

Example 22

The therapeutic efficacy of the transdermal devices elaborated as in Example 2 was applied in 9 patients

suffering knee osteoarthritis. The trial had an open design and the patients were required to indicate the degree of pain on a graphic scale (Visual Analogue Scale method [4]). The results are shown in Table 2.

5

TABLE 2

Parameter	Percent of Pain reduction from baseline	
	Period of control (7 days)	Transdermal device according to Example 2
		7 days 14 days
Spontaneous pain	21.8	56.6 64.5
Pain on movement	4.5	45 55.3
Pain on pressure	2.6	43.7 48.4
Post-resting rigidity	8.3	66.7 83.3

20

During the period of control the patients were only medicated with oral paracetamol. The applied devices contained 100 mg of DDA in a surface of 100 cm² and were replaced each 24 hours.

25

Example 23

Experiment with a design similar to the one of Example 22 using a device elaborated as in Example 4. The participating patients (n = 7) had the same pathology.

30

The results are shown in Table 3.

TABLE 3

Parameter	Period of control (7 days)	Percent of Pain reduction from baseline	
		Transdermal device according to Example 4	
		7 days	14 days
Spontaneous pain	5.4	24.9	43.8
Pain on movement	9.6	26.6	40
Pain on pressure	8.1	18.8	35.9

The applied devices contained 100 mg of DDA in a surface of 100 cm² and were replaced every 24 hours.

Example 24

Experiment with a design similar to Example 23 using a device elaborated as in Example 4, performed over 33 patients with the same pathology. The results are shown in Table 4.

TABLE 4

Parameter	Period of control (7 days)	Percent of Pain reduction from baseline	
		Transdermal device according to Example 4	
		7 days	14 days
Spontaneous pain	8.5	34.8	49.1
Pain on movement	9.3	31.8	50.4
Pain on pressure	9.2	35.9	51.6
Post-resting rigidity	4.4	46.8	45.4

In this case, the applied devices contained 100 mg of DDA in a surface of 50 cm². The transdermal devices were replaced each 24 hours.

Example 25

The plasmatic levels of diclofenac obtained after the second application of a transdermal device similar to the one used in Example 24 were determined in 14 healthy volunteers. The samples were measured by GC-MS and the results are shown in Table 5.

TABLE 5

Time after the second application (hours)	4	12	24
Plasmatic concentration of diclofenac (nmol/liter)	47.8 (7.6) *	40.0 (5.1) *	34.7 (4.8) *

*Standard Error of the Mean (SEM)

These results show that the transdermal device brings low (compared with the oral or injectable dosage forms), but steady plasmatic concentrations of the active drug.

References

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CLAIMS

1. A transdermal administration device that contains:

- 5 (a) a pharmaceutical composition for the systemic administration of a NSAID;
(b) a backing layer; and,
(c) a release liner;
wherein said pharmaceutical composition
10 includes at least one component that enhances percutaneous permeation selected from:

- (i) fatty alcohols (C₄-C₃₀);
(ii) mono, di or triglyceryl fatty
acid esters (C₄-C₃₀); and,
15 (iii) fatty acid esters (C₄-C₃₀);
and a pressure sensitive acrylic adhesive matrix formed by a copolymer with polar functional groups in which the NSAID is incorporated.

20

2. A transdermal administration device according to claim 1, wherein the NSAID is selected from the group consisting of diclofenac, indomethacin, piroxicam, meloxicam, and pharmaceutically acceptable
25 salts thereof, and is present in an amount in the range 4.5 to 32% by weight of total content excluding adhesive solvents.

3. A transdermal administration device according

to claim 2, wherein the NSAID is the diclofenac diethylammonium salt.

4. A transdermal administration device according
5 to any one of claims 1 to 3, wherein the pressure
sensitive adhesive matrix contains methacrylic acid or
an ester thereof, at least one other copolymerisable
monomer and cross-linking agent, and said pressure
sensitive adhesive polymeric matrix is present in an
10 amount in the range 50 to 97.5% by weight of total
content excluding adhesive solvents.

5. A transdermal administration device according
to claim 4, wherein the pressure sensitive acrylic
15 mixture is a copolymer of 2-ethyl-hexyl-acrylate,
methyl-acrylate, acrylic acid, and
glycidylmethacrylate.

6. A transdermal administration device according
20 to any one of claims 1 to 5, wherein the permeation
enhancer is oleyl alcohol, and is present in an amount
in the range 5.5 to 35% by weight of total content
excluding adhesive solvents.

25 7. A transdermal administration device according
to any one of claims 1 to 5, wherein the permeation
enhancer is isopropyl myristate, and is present in an
amount in the range 5.5 to 35% by weight of total
content excluding adhesive solvents.

8. A transdermal administration device according to any one of claims 1 to 5, wherein the permeation enhancer is glyceryl monooleate, and is present in an amount in the range 5.5 to 35% by weight of total
5 content excluding adhesive solvents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/00707

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K9/70 A61K47/10 A61K47/14 A61K31/196 A61K31/405 A61K31/5415 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 94 15609 A (SUNKYONG IND LTD ;MIN DONG SON (KR); UM KEE AN (KR); KIM YONG SOO) 21 July 1994 (1994-07-21) figures 1,2; examples 1,3 claims 1,2,6-10 --- <div style="text-align: center;">-/-</div>	1,2,4
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">19 June 2000</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">27/06/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Epskamp, S</div>

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